REMARKS

I. The Amendments

The claims have been amended, without prejudice, for the purpose of more clearly defining what Applicants regard as the invention and for placing the rejected claims in condition for allowance. These amendments do not add new matter and are fully supported in the specification and the claims as originally filed. Therefore, entry of the amendments under 37 C.F.R. § 1.111 is respectfully requested.

Marked up copies of the claims are presented in *Appendix A*. The currently pending claims are presented in *Appendix B*.

II. The Rejections

A. The Rejection Of Claims 8, 9, 16, and 17 Under 35 U.S.C. § 112, First Paragraph

Claims 8, 9, 16, and 17 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is respectfully traversed.

The presently claimed invention encompasses a method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of a protease-related protein, wherein said protease-related protein is encoded by a nucleotide sequence hybridizing with the complement of the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting. *See*, *e.g.*, Claim 8.

The Examiner acknowledges that the specification provides guidance and examples for making a protease-related protein consisting of the amino acid sequence of SEQ ID NO:2 or encoded by the polynucleotide consisting SEQ ID NO:1, however, he asserts that teaching

of the addition, deletion or substitution of specific amino acid residue(s) or base pairs, or combinations thereof in SEQ ID NO:2 or SEQ ID NO:1 to make a protein that still retains the desired activity is lacking. Applicants respectfully disagree.

The specification teaches that administration of the protease-related protein (also referred to as PVP) of the invention (in the form of protein or as nucleic acid encoding and expressing the same) leads to a downregulation of keratinization of hair. *See*, Substitute Specification, at page 2, lines 19-26 and page 5, lines 6-14. Downregulation of keratinization of hair can be readily detected in the changed chemical composition of hair. Moreover, downregulation of keratinization will ultimately lead to hair loss, which can be readily detected. Thus, there are tests available to determine whether a protein comprising amino acid or base pair additions, deletions or substitutions relative to the amino acid sequence of SEQ ID NO:2 would be a protease-related protein according to the present invention. Thus, one skilled in the art would be able to determine without undue experimentation whether a particular sequence variant could be used for the methods and compositions presently claimed. Accordingly, the recited sequence variations of the protease-related proteins of the invention are enabled, and this aspect of the rejection under 35 U.S.C. § 112, first paragraph is in error and should be withdrawn.

In a further aspect of the rejection for lack of enablement, the Examiner, while acknowledging that the specification discloses administering the claimed "protease-related protein" would be used in the "negative regulation of the keratinization of hair," asserts that the specification fails to demonstrate a distinct and well defined relationship between the claimed "protease-related protein" and the "keratinization of hair." The Applicants respectfully disagree.

In the specification the Applicants teach that there is a causal relationship between the presence of PVP and the absence of hair. Specifically, the Applicants teach that PVP is upregulated in nude whn (-/-) mice. In particular, the Applicants found that the absence of the whn gene results in upregulation of PVP, while the expression of keratin (encoded by Ha3 and CK15) is downregulated. *See*, Substitute Specification, *e.g.*, at page 2, lines 24-26. Thus, it can be concluded that the upregulation of PVP is promoting the lack of hair. Accordingly, the Examiner's statement that "the specification fails to demonstrate a distinct and well defined relationship between the claimed 'protease-related protein' and the 'keratinization of hair'" is mistaken and this ground for a rejection for lack of enablement should be withdrawn.

In a further aspect of the enablement rejection, the Examiner states that the Applicants fail to show that administration of the claimed "protease-related protein" to a patient does not harm the patient. Applicants respectfully point out that for purposes of patentability they are not required to demonstrate that PVP is a safe drug.

Specifically, it is respectfully pointed out that any toxic effects of a drug candidate is evaluated in clinical trials administered in connection with an application for Food and Drug Administration (FDA) approval. It is understood that a drug can only be useful if it is safe. The safety of a drug is determined during the FDA approval process in that what is known as Phase I and Phase II studies. On the basis of animal studies and controlled testing on a limited number of humans (referred to as Phase I testing), the FDA may authorize Phase II clinical studies. Authorization of a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. 21 C.F.R.

§§ 312.21(b); 312.23(a)(5), (a)(8); 21 U.S.C. 355(i)(1). *See*, also, *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995).

However, FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott v. Finney*, 34 F.3d 1058, 1063; 32 USPQ2d 1115, 1120. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Therefore, this ground for a rejection for lack of utility/enablement is not in line with the generally applied legal standard and should therefore be withdrawn.

As a final aspect of the enablement rejection, the Examiner objects to the recitation of "administering a therapeutically effective amount" of the claimed protease-related protein as being unpredictable in the absence of *in vivo* data because (1) the peptide/polypeptide may be inactivated before producing an effect due to proteolytic degradation or immunological inactivation or the inherently short half-life of the peptide/polypeptide; (2) the peptide/polypeptide may not reach the target area because, *e.g.*, the peptide/polypeptide may not be able to cross the mucosa or the peptide/polypeptide may be absorbed by fluids, cells and tissues where the peptide/polypeptide has no effect; and (3) other functional properties, known or unknown, may make the peptide/polypeptide unsuitable for *in vivo* therapeutic use, *i.e.*, such as adverse side effects which prohibit the use of the peptide for the "negative regulation of the keratinization of hair." Applicants respectfully point out that they are not required to show the specific efficacy of PVP.

As pointed out above, the legal standard for usefulness and enablement of a claimed invention does not require that the Applicant for a patent shows safety and efficacy of a compound in humans. It is the purpose of Phase II clinical studies that have been authorized

by the FDA to make this determination. Indeed, as the Federal Circuit cautions in *In re Brana, supra*, "[w]ere we to require Phase II testing in order to prove utility[1], the associated costs would prevent companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer." Thus, this aspect for a rejection for lack of enablement/utility is improper and should be withdrawn.

In view of the above, the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

B. The Rejection of Claims 8, 9, 16, and 17 Under 35 U.S.C. § 112, Second Paragraph

Claims 8, 9, 16, and 17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is in part obviated and/or overcome in view of the amendments to the claims, and in part traversed.

First, the phrase "protease-related protein" in Claim 8 is objected to as being indefinite "because the meaning of the phrase is not known." This rejection is respectfully traversed. Applicants wish to point out that the term "protease-related protein" is the designation the Applicants chose for the class of proteins used for the methods of the presently claimed invention. As defined in the specification, the class of "protease-related proteins" used for the methods of the present invention is characterized by having homologies with a protease of the kallikrein family, and that it further optionally has a protease activity. The protease-related protein of the invention is further defined by comprising the amino acid sequence of FIGURE 1, or being homologous to the same. *See*, Substitute Specification, at

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[1] Although the court refers to utility, the court argument was made in the context of a rejection under 35 U.S.C. § 112, first paragraph, as in the present case.

page 16, lines 16 through 20. Thus, the specification clearly defines what is encompassed by the phrase "protease-related protein," and accordingly the rejection should be withdrawn.

Second, the phrase "wherein the protein is present as such or in the form of a nucleic acid" in Claim 9 is objected to as being indefinite. This rejection is obviated and/or overcome in view of the amendment to Claim 9 and therefore should be withdrawn.

Third, the phrase "a DNA hybridizing" in Claims 16 and 17 is objected to because the specific hybridization conditions are not recited in the claims. This rejection is obviated and/or overcome in view of the amendment to Claims 16 and 17 and therefore should be withdrawn.

Forth, the phrase "via the degenerated genetic code" in Claim 16 and 17 is objected to as being indefinite. This rejection is obviated and/or overcome in view of the amendment to Claims 16 and 17 and therefore should be withdrawn.

CONCLUSION

In view of the above remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 (order no. 8484-081-999) for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date February 21, 2002

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APPENDIX A
Marked-up Version of the Amended Claims
Serial No. 09/486,247

8. (Twice amended) A method for the negative regulation of the keratinization of hair, comprising administering [in] a therapeutically effective amount of a protease-related protein, [said protein comprising the amino acid sequence (SEQ ID NO:2) or an amino acid sequence differing therefrom by one or more amino acids] wherein said protease-related protein is encoded by a nucleotide sequence hybridizing with the complement of the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting.

9. (Twice amended) The method of Claim 8, wherein [the] said protease-related protein is [present as such or] administered in the form of a nucleic acid expressing it.

16. (Amended) The method of Claim 9 or 18, wherein said nucleic acid expressing said protein comprises:

(a) the [DNA] nucleotide sequence of [FIGURE 1 or a DNA differing therefrom by one or more base pairs] SEQ ID NO:1;

(b) a [DNA] nucleotide sequence hybridizing [with the complement of the DNA of (a)] to the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting; [or]

(c) a [DNA related to the DNA of (a) or (b) via the degenerated genetic code] nucleic acid encoding the same amino acid sequence as the nucleic acid sequence of (a) or (b), but having a different nucleotide composition due to the degenerated genetic code; or

(d) the complement of (a), (b), or (c).

17. (Amended) The method of Claim 9 or 18, wherein said nucleic acid expressing said protein comprises an expression plasmid comprising:

(a) the [DNA] nucleotide sequence of [FIGURE 1 or a DNA differing therefrom by one or more base pairs] SEQ ID NO:1;

APPENDIX B
Clean Version of the Amended Claims
Serial No. 09/486,247

8. (Twice amended) A method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of a protease-related protein, wherein said protease-related protein is encoded by a nucleotide sequence hybridizing with the complement of the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting.

9. (Twice amended) The method of Claim 8, wherein said protease-related protein is administered in the form of a nucleic acid expressing it.

16. (Amended) The method of Claim 9 or 18, wherein said nucleic acid expressing said protein comprises:

(a) the nucleotide sequence of SEQ ID NO:1;

(b) a nucleotide sequence hybridizing to the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting;

(c) a nucleic acid encoding the same amino acid sequence as the nucleic acid sequence of (a) or (b), but having a different nucleotide composition due to the degenerated genetic code; or

(d) the complement of (a), (b), or (c).

17. (Amended) The method of Claim 9 or 18, wherein said nucleic acid expressing said protein comprises an expression plasmid comprising:

(a) the nucleotide sequence of SEQ ID NO:1;

(b) a nucleotide sequence hybridizing to the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting;

(c) a nucleic acid encoding the same amino acid sequence as the nucleic acid sequence of (a) or (b), but having a different nucleotide composition due to the degenerated genetic code; or

(d) the complement of (a), (b), or (c).

(b) a [DNA] nucleotide sequence hybridizing [with the complement of the DNA of (a)] to the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting; [or]

(c) a [DNA related to the DNA of (a) or (b) via the degenerated genetic code] nucleic acid encoding the same amino acid sequence as the nucleic acid sequence of (a) or (b), but having a different nucleotide composition due to the degenerated genetic code; or

(d) the complement of (a), (b), or (c).

18. (New) The method of Claim 8, comprising administering a polynucleotide encoding said protease-related protein and expressing a therapeutically effective amount of the same.

19. (New) A composition for the negative regulation of the keratinization of hair comprising a protease-related protein and a pharmaceutically acceptable carrier, wherein said protease-related protein is encoded by a nucleotide sequence hybridizing with the complement of the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting.

20. (New) The composition of Claim 19, wherein said protease-related protein comprises the amino acid sequence of SEQ ID NO:2.

21. (New) A method for the negative regulation of the keratinization of hair comprising administering a therapeutically effective amount of a protease-related protein, wherein said protease-related protein comprises the amino acid sequence of SEQ ID NO:2.

22. (New) A method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of the composition of Claim 19.

23. (New) A method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of the composition of Claim 20.

18. (New) The method of Claim 8, comprising administering a polynucleotide encoding said protease-related protein and expressing a therapeutically effective amount of the same.

19. (New) A composition for the negative regulation of the keratinization of hair comprising a protease-related protein and a pharmaceutically acceptable carrier, wherein said protease-related protein is encoded by a nucleotide sequence hybridizing with the complement of the nucleotide sequence of SEQ ID NO:1 at 20°C below the DNA melting.

20. (New) The composition of Claim 19, wherein said protease-related protein comprises the amino acid sequence of SEQ ID NO:2.

21. (New) A method for the negative regulation of the keratinization of hair comprising administering a therapeutically effective amount of a protease-related protein, wherein said protease-related protein comprises the amino acid sequence of SEQ ID NO:2.

22. (New) A method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of the composition of Claim 19.

23. (New) A method for the negative regulation of the keratinization of hair, comprising administering a therapeutically effective amount of the composition of Claim 20.